Environment International 114 (2018) 152–159

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Prenatal urinary triclosan concentrations and child neurobehavior

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ARTICLE INFO

Keywords:
Triclosan
Prenatal exposure
Child neurobehavior
Children's environmental health

ABSTRACT

Background: Exposure to triclosan, an antimicrobial chemical, is ubiquitous among pregnant women and may reduce thyroid hormone levels that are important for fetal neurodevelopment. Few studies have examined the association between prenatal triclosan exposure and children's neurobehavior.
Objective: We investigated the relationship of prenatal urinary triclosan concentrations with children's behavior and cognitive abilities at age three years in a prospective pregnancy and birth cohort in Canada.
Methods: We measured triclosan in urine samples collected at ~12 weeks of gestation in 794 Canadian women enrolled in a prospective pregnancy and birth cohort study (MIREC) from 2008 to 2011. Around age 3 years, we assessed children's cognitive abilities using the Wechsler Primary and Preschool Scale of Intelligence-III (WPPSI-III), and two scales of the Behavior Rating Inventory of Executive Function-Preschool (BRIEF-P). Parents reported children's problem and reciprocal social behaviors using the Behavior Assessment System for Children-2 (BASC-2) and Social Responsiveness Scale-2 (SRS-2), respectively.
Results: After adjusting for confounders using multivariable linear regression, triclosan was not associated with most of the 30 examined neurobehavioral scales. Each 10-fold increase in triclosan was associated with better WPPSI-III picture completion scores (β: 0.2; 95% CI: 0,0.5) and BASC-2 externalizing (β: −0.5; 95% CI: −1.1, 0) and hyperactivity (β: −0.6; 95% CI: −1.2, −0.1) scores, suggesting less externalizing and hyperactive behaviors. Child sex did not modify these associations.
Conclusions: In this cohort, urinary triclosan concentrations measured once in early pregnancy were not associated with most assessed aspects of neurobehavior and weakly associated with a few others, but not in the hypothesized direction.

1. Introduction

Triclosan is an antimicrobial chemical used in some personal care and consumer products. The U.S. Food and Drug Administration banned triclosan in over-the-counter consumer wash products in 2016 in part because of concerns about its developmental toxicity (Safety and Effectiveness of Consumer Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use, 2016); however, other sources of triclosan exposure remain in commerce, including some toothpastes, body lotions, cosmetics, toys, textiles, and kitchenware (Dann and Hontela, 2011; Rodricks et al., 2010). Triclosan is detected in the urine of > 80% of pregnant women in North America, indicating nearly ubiquitous exposure among this sensitive population (Woodruff et al., 2011; Etzel et al., 2017; Arbuckle et al., 2015a).

Prenatal triclosan exposure may adversely impact fetal neurodevelopment by affecting the hypothalamic-pituitary-thyroid axis during gestation (Brucker-Davis, 1998). Thyroid hormones play a critical role in fetal growth and neurodevelopment (de Escobar et al., 2004;

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https://doi.org/10.1016/j.envint.2018.02.032
Received 13 November 2017; Received in revised form 30 January 2018; Accepted 20 February 2018
Available online 02 March 2018

Ghassabian et al., 2011; Gilbert et al., 2012; Zoeller and Rovet, 2004; Henrichs et al., 2010; Korevaar et al., 2016; Ghassabian et al., 2012; Andersen et al., 2014; Modesto et al., 2015; Brown et al., 2015; Lyall et al., 2016; Yau et al., 2015) and reduced levels of thyroid hormones during gestation can affect fetal neurodevelopment, which in turn may increase the risk of cognitive and motor deficits, as well as behavioral disorders. Rodent studies show that triclosan exposure can reduce thyroxine concentrations in pregnant, fetal, and juvenile rats (Johnson et al., 2016; Paul et al., 2012; Paul et al., 2010). Two epidemiological studies found an inverse association of prenatal urinary triclosan concentrations with maternal and cord blood thyroxine and triiodothyronine levels (Wang et al., 2017; Braun et al., 2017a). In addition, in vitro studies show that triclosan exposure induces apoptosis in neocortical neurons (Szychowski et al., 2015; Szychowski et al., 2016).

We are not aware of any animal studies examining the neurotoxicity of triclosan exposure; one epidemiological study found no association between prenatal triclosan exposure and children's visual-spatial abilities (Braun et al., 2017b). Given the potential for triclosan to disrupt thyroid hormone homeostasis, we investigated the relationship of prenatal urinary triclosan concentrations with children's behavior and cognitive abilities at age three years in a prospective pregnancy and birth cohort in Canada.

2. Materials and methods

2.1. Study participants

We used data from the Maternal-Infant Research on Environmental Chemicals (MIREC) study, a prospective pregnancy and birth cohort of 2000 pregnant women from ten cities (11 study sites) across Canada. Details about eligibility, recruitment, and follow-up are previously described (Arbuckle et al., 2013). Briefly, we recruited pregnant women during the first trimester of pregnancy from obstetric and prenatal clinics between 2008 and 2011. Women must have planned on delivering at a local hospital, been able to communicate in English or French, been ≥18 years of age, and agreed to participate in the cord blood collection component of the MIREC study. We excluded women if they had a history of major chronic disease, illicit drug use, threatened abortion, or were carrying a fetus with a known malformation or abnormality. Among 8716 women we approached to participate in MIREC, 5108 (58.6%) were eligible, 1983 (38.8%) consented and participated, and 1861 had singleton lives births.

The ethics review boards or committees from Québec and Sainte-Justine research centers, Health Canada, and participating recruitment sites approved this research. We provided potential participants with information about the student design and objectives before asking them to sign informed consent forms for the prenatal and child follow-up part of the study.

2.2. Prenatal triclosan exposure assessment

At an average of 12.1 weeks gestation (range: 5.1–15.0) we collected a single urine sample from women. Samples were aliquoted and frozen at −20 °C within 2 h of collection, and later shipped on dry ice to the MIREC coordinating center in Montréal where they were stored at −30 °C. For triclosan analysis, urine samples were shipped to the Centre de toxicologie du Québec, Institut National de Santé Publique du Québec. We quantified total (conjugated + free) triclosan concentrations using gas chromatography coupled with tandem mass spectrometry (GC–MS/MS) (Arbuckle et al., 2015b). Field blanks were used to assess for potential exogenous contamination from the materials used for urine specimen collection and storage, and from the environment of the collection sites. All field blanks were free of triclosan contamination. Several quality control samples, reagents blanks, and urine blanks were incorporated into each batch of samples (Arbuckle et al., 2015b). The intraday precision ranged from 2.5% to 7.7%, and the interday precision ranged from 4.3% to 13%.

We measured urine specific gravity (SG) with a refractometer and used SG to account for individual variation in urine dilution by SG-standardizing urinary triclosan concentrations with the following formula (Duty et al., 2005):

$$P_s = P_i\left(\frac{SG_m - 1}{SG_i - 1}\right)$$

where P_s is the SG-standardized triclosan concentration, P_i is the observed triclosan concentration for the i-th woman, SG_m is the median SG (1.013), and SG_i is the observed SG for the i-th woman. We $\log_{10}$-transformed SG-standardized urinary triclosan concentrations to reduce the influence of extreme observations.

2.3. Child follow-up and neurobehavior assessments

We conducted follow-up on 896 (46.9%) singleton children from all MIREC study sites when they were approximately 3 years old (mean: 3.4 years; range: 2.8–4.2). Among these, 794 had urinary triclosan concentrations measured at about 12 weeks, complete covariate data, and internet questionnaire-based assessments of neurobehavior (Supplemental Table 1; Supplemental Fig. 1). We conducted additional in-person neurobehavioral assessments of 531 (27.8%) children with complete data from the 7 most populous MIREC study sites (Supplemental Table 1; Supplemental Fig. 1). At this visit, trained research personnel measured child anthropometry, collected children's blood and urine, and administered questionnaires to the parents and neurobehavioral assessments to the child. Minor variations in the sample size arose from invalid administration of in-person tests (e.g., inadequate test environment) or incomplete questionnaires (e.g., parent did not complete surveys). Because of limited resources, we were unable to conduct follow-up on all MIREC study participants and only conducted follow-up on children who were in our target age range (~3–4 years) during the follow-up phase of this study. Thus, our follow-up rates reflect this, as well as loss to follow-up.

We assessed child neurobehavior with standardized and age-appropriate tests described below because previous studies report that the traits they measure are associated with prenatal environmental chemical exposures, including chemicals that may disrupt thyroid function (Dietrich et al., 2005; Chen et al., 2014; Vuong et al., 2015). These tests are routinely used in studies of developmental neurotoxicants (Dietrich et al., 2005). Additionally, performance on or behaviors measured by some of these tests have been associated with alterations in maternal thyroid function during pregnancy (Ghassabian et al., 2011; Korevaar et al., 2015). Finally, these tests provide a broad assessment of child neurobehavior, including omnibus features like child cognitive abilities (i.e., IQ), as well as specific features of clinical disorders like attention-deficit/hyperactivity disorder (ADHD) (e.g., externalizing behaviors) and autism spectrum disorder (ASD) (e.g., affect recognition).

Caregivers completed the Behavioral Assessment System for Children-2 (BASC-2) and two subscales from the Behavior Rating Inventory of Executive Function-Preschool (BRIEF-P) using paper-and pencil versions or an internet-based platform. The BASC-2 is a reliable and valid 134-item assessment of children's problem behaviors in home and community settings (Reynolds and Kamphaus, 2002). The BASC-2 include three composite scores that measure children's total (Behavioral Symptom Index [BSI]), internalizing, and externalizing behavior problems, as well as eight clinical subscales (attention, atypicality, aggression, anxiety, depression, hyperactivity, somatization, and withdrawal). Children's executive function were assessed by caregiver report using 27 items from the working memory and plan/organize subscales of the BRIEF-P (Gioia et al., 2003).

During the in-person assessment, children who were between the ages of 36 and 47 months completed the Receptive Vocabulary, Information, Block Design, Object Assembly, and Picture Naming

subtests of the Wechsler Preschool and Primary Scale of Intelligence-III (WPPSI-III) and all children completed the Affect Recognition subtest of the A Developmental Neuropsychological Assessment-II (NEPSY-II). The WPSSI-III is a reliable and valid assessment of children's cognitive abilities (Wechsler, 2002). In the Affect Recognition test, children are asked to identify emotions from photographs of children's faces and scores on this test reflect visual attention, visual discrimination, and facial recognition (Korkman et al., 2007).

Caregivers completed the Social Responsiveness Scale-2 (SRS-2) during the in-person assessment. The SRS-2 is a valid and reliable 65-item assessment that assesses communication, interpersonal behaviors, and repetitive or stereotypic behaviors. It provides a summary scale, five subscales (social cognition, social communication, social awareness, social motivation, and restricted interests and repetitive behaviors), and two scales related to the Diagnostic and Statistical Manual-V diagnostic criteria for autism spectrum disorders (Bolte et al., 2008).

Study staff from each participating study site completed a 3-day training session that was led by a PhD-level psychologist (E.O.) and focused on specialized training of these assessment tools. The training emphasized the importance of providing an ideal and standardized environment in the home by ensuring that the test area was well-lit, quiet, and free from distractions and interruptions. A single staff person from each study site administered in-person assessments. At the time of child assessment, both study staff and caregivers were blinded to mother's triclosan concentrations during pregnancy.

Using software provided by test publishers and United States population-based normative data, we calculated full-scale IQ (FSIQ), performance IQ (PIQ), and verbal IQ (VIQ) scores, as well as subtest scores for the WPPSII-III. Higher WPPSII-III scores indicate better performance. The same methods were used to calculate T-scores for the BASC-2, BRIEF-P, and SRS-2. For BASC-2, BRIEF-P, and SRS-2 higher T-scores indicate poorer functioning and more of those behaviors. Finally, we calculated scaled Affect Recognition test scores, where higher scores indicate better recognition of facial expressions, visual attention, and visual discrimination.

2.4. Covariates

Trained research assistants administered standardized interviews during the 1st and 3rd trimesters to assess potential confounders. These included maternal race, education, age at delivery, household income, employment, parity, and self-reported alcohol consumption and smoking during pregnancy. Additionally, caregivers completed standardized questionnaires at the time of child assessment that measured maternal depressive symptoms (Center for Epidemiological Studies-Depression Scale 10), parenting stress (Parenting Relationship Questionnaire), the duration of breastfeeding, caregiver-reported delinquent behavior during adulthood, and whether the child received any regularly scheduled daycare. Finally, during in-person visits, the HOME Inventory was administered, a semi-structured interview that measures the quality and quantity of the caregiving environment (Bradley et al., 1988).

We used directed acyclic graphs (DAGs) to identify variables that were potential causes of both urinary triclosan concentrations and at least one neurobehavioral outcome (Stacy et al., 2017), but not variables that were colliders or causal intermediates (Supplemental Fig. 2). All analyses were adjusted for maternal race, education, age, household income, employment, marital status, parity, smoking during pregnancy, alcohol use during pregnancy, parental stress, maternal depressive symptoms, and months of exclusive breastfeeding.

2.5. Statistical methods

First, we described the central tendency of urinary triclosan concentrations and children's BSI, FSIQ, and SRS-2 total scores by covariates. Then, using natural splines, we tested for non-linear relations between urinary triclosan concentrations and neurobehavioral scores. Using multivariable linear regression, we estimated the unadjusted and covariate-adjusted associations between $\log_{10}$-transformed SG-standardized urinary triclosan concentrations and neurobehavioral test scores. To further characterize dose-response relations, we estimated the adjusted mean of summary scale scores from BASC-3 and WPPSI-III, SRS-2 total, and NEPSY: Affect recognition in relation to quintiles of urinary triclosan concentrations. We estimated sex-specific associations among boys and girls using product interaction terms between child sex and urinary triclosan concentration variables. We considered modification to be present when the triclosan × child sex p-value was ≤ 0.10.

To examine the impact of adjusting for study site, we compared models that did not adjust for study site, included study site as a covariate, or used generalized estimating equations (GEEs) to account for study site. Adjusting for study site did not meaningful change our results and we ultimately decided to not adjust for study site.

2.6. Sensitivity analysis

To evaluate the robustness of our results, we conducted several sensitivity analyses. First, prior studies have shown that folic acid supplementation during early pregnancy may have beneficial effects on neurodevelopment beyond its effect on neural tube defect prevention, including mitigating the effect of some neurotoxicant exposures (Gao et al., 2016; Schmidt et al., 2017). Among women with reported supplement use during the first trimester of pregnancy, we examined whether taking any vs. no folic acid supplements modified the association between prenatal urinary triclosan concentrations and neurobehavioral outcomes by including a product interaction term between triclosan concentration × folic acid supplementation. Second, we compared the results from models that did and did not adjust for covariates that were measured at the child-follow up visit because covariates at the child follow-up visit occurred after exposure and may not be associated with prenatal urinary triclosan concentrations. Third, we adjusted for maternal receipt of welfare support (n = 17). Fourth, among children who completed the in-person visit, we adjusted for daycare attendance and HOME Inventory. We compared results from models adjusted for primary covariates and primary covariates plus daycare attendance and HOME inventory scores among the subset of children who completed the in-person follow-up to avoid potential selection biases that result from not completing the in-person follow-up. Fifth, because there can be additional age-related variation in behavior and cognition that is not captured by the test developer's standardization, we also adjusted for child age. Finally, we examined if our method of measuring urine dilution influenced our results by comparing models that used creatinine-standardized urinary triclosan concentrations to those that used SG-standardized triclosan concentrations.

3. Results

Women in the MIREC study generally were white (86%), > 25–35 years of age (61%), married or living with a partner (98%), employed (89%), university educated (69%), of higher income (> $100 K, 41%), non-smokers during pregnancy (96%), and non-consumers of alcohol during pregnancy (55%) (Table 1).

The median urinary triclosan concentration during pregnancy was 8.8 ng/mL (range: < LOD-2621 ng/mL), with 0.4% of samples having concentrations below the LOD. We observed a bimodal distribution of $\log_{10}$-transformed SG-standardized urinary triclosan concentrations where the median within each mode was approximately 6.5 and 300 ng/mL (Supplemental Fig. 3). Median urinary triclosan concentrations were higher among pregnant women who were > 25–35 years of age, white, had a graduate degree, not married or living alone, employed, had a household income greater than $100,000 (CAD), and had 2 or more children (Table 1). Median SG-standardized urinary triclosan concentrations during pregnancy were 8.9 ng/mL, 8.8 ng/mL,

Table 1
Central tendency and variation of specific gravity standardized maternal urinary triclosan concentrations during pregnancy and child BASC-2 BSI, SRS-2 total, and WPPSI-III FSIQ scores at three years of age according to covariates: the MIREC study.

Variable	Triclosan (ng/mL)			BSI			SRS-2			FSIQ		
	N	%	Median (25th,75th)	N	%	Mean (SD)	N	%	Mean (SD)	N		Mean (SD)
Overall	794	–	8.8 (2.5, 107)	790	–	51 (7)	524	–	45 (6)	528	–	107 (14)
Maternal age												
18–25 years	25	3.1	6.4 (2.5, 67)	25	3.2	50 (5)	14	2.7	48 (7)	15	2.8	103 (12)
> 25–35 years	486	61.2	9.1 (2.6, 105)	483	61.1	51 (7)	332	63.4	46 (6)	333	63.1	107 (14)
> 35 years	283	35.6	8.3 (2.3, 113)	282	35.7	50 (7)	178	34.0	45 (6)	180	34.1	108 (14)
Maternal race												
White	687	86.5	9.4 (2.5, 117)	685	86.7	51 (7)	452	86.3	45 (6)	452	85.6	108 (13)
Asian/Pacific Islander	26	3.3	8.7 (1.9, 73)	26	3.3	52 (6)	14	2.7	46 (5)	15	2.8	110 (11)
Other	47	5.9	4.5 (1.8, 54)	45	5.7	51 (8)	34	6.5	48 (6)	37	7.0	97 (15)
Multi-racial	34	4.3	6.8 (2.6, 19)	34	4.3	50 (6)	24	4.6	46 (6)	24	4.5	107 (15)
Maternal education												
Graduate degree	226	28.5	12 (2.5, 176)	226	28.6	50 (6)	144	27.5	44 (5)	145	27.5	110 (12)
University degree	318	40.1	9.2 (2.5, 86)	317	40.1	51 (7)	215	41.0	45 (7)	216	40.9	108 (14)
Some college, trade school, or diploma	208	26.2	6.6 (2.2, 86)	205	25.9	51 (7)	142	27.1	46 (6)	143	27.1	103 (14)
High school or less	42	5.3	9.9 (2.7, 119)	42	5.3	51 (8)	23	4.4	47 (7)	24	4.5	99 (11)
Marital status												
Married or living with partner	774	97.5	8.8 (2.5, 108)	771	97.6	51 (7)	508	96.9	45 (6)	512	97.0	107 (14)
Not married or living alone	20	2.5	9.5 (2.9, 79)	19	2.4	54 (9)	16	3.1	50 (7)	16	3.0	102 (15)
Household income (CAD)												
> $100 K	322	40.6	13 (3.1, 165)	321	40.6	50 (7)	209	39.9	44 (6)	211	40.0	109 (13)
$80 K–100 K	266	33.5	6.5 (1.9, 58)	265	33.5	51 (7)	171	32.6	45 (6)	172	32.6	107 (14)
$40 K– < 80 K	132	16.6	6.7 (2.2, 48)	130	16.5	51 (6)	90	17.2	46 (7)	91	17.2	104 (14)
< $40 K	74	9.3	11 (2.5, 64)	74	9.4	53 (8)	54	10.3	48 (6)	54	10.2	104 (14)
Employment												
No	91	11.5	6.6 (2.2, 28)	91	11.5	52 (8)	59	11.3	47 (9)	59	11.2	102 (17)
Yes	703	88.5	9.2 (2.5, 114)	699	88.5	50 (7)	465	88.7	45 (6)	469	88.8	108 (13)
Parity												
0	351	44.2	9.1 (2.7, 119)	349	44.2	51 (7)	231	44.1	46 (6)	234	44.3	109 (14)
1	326	41.1	8.3 (2.2, 94)	324	41.0	51 (7)	214	40.8	45 (6)	214	40.5	106 (14)
2+	117	14.7	9.2 (2.8, 93)	117	14.8	50 (6)	79	15.1	45 (7)	80	15.2	104 (12)
Smoking during pregnancy												
No	765	96.3	8.8 (2.5, 100)	761	96.3	51 (7)	508	96.9	45 (6)	512	97.0	107 (14)
Yes	29	3.7	6.7 (1.7, 140)	29	3.7	51 (9)	16	3.1	49 (7)	16	3.0	98 (16)
Alcohol use during pregnancy												
No	439	55.3	8.1 (2.5, 85)	436	55.2	51 (6)	299	57.1	45 (6)	302	57.2	106 (14)
Yes	355	44.7	9.2 (2.4, 117)	354	44.8	50 (7)	225	42.9	45 (6)	226	42.8	108 (13)
Duration of exclusive breastfeeding												
≥6 months	405	51.0	9.6 (2.6, 111)	404	51.1	51 (6)	260	49.6	45 (6)	262	49.6	109 (13)
< 6 months	389	49.0	8 (2.3, 99)	386	48.9	51 (7)	264	50.4	46 (7)	266	50.4	105 (14)
Parenting stress[a]												
< 1 SD	667	84.0	9 (2.5, 108)	666	84.3	49 (6)	438	83.6	44 (5)	440	83.3	108 (13)
≥1 SD	127	16.0	8 (2.0, 85)	124	15.7	57 (7)	86	16.4	52 (8)	88	16.7	102 (17)
Maternal CES-D score												
< 16	768	96.7	8.8 (2.5, 105)	765	96.8	50 (7)	505	96.4	45 (6)	509	96.4	107 (14)
≥16	26	3.3	8.3 (2.0, 211)	25	3.2	54 (7)	19	3.6	48 (5)	19	3.6	107 (12)
Child sex												
Male	389	49.0	7.6 (2.0, 73)	387	49.0	51 (7)	254	48.5	46 (7)	258	48.9	104 (15)
Female	405	51.0	9.5 (2.7, 125)	403	51.0	50 (6)	270	51.5	44 (5)	270	51.1	109 (12)
Folic acid supplement during pregnancy												
No	80	10.7	8.8 (2.1, 95)	80	10.8	51 (6)	353	67.4	46 (7)	50	10.2	106 (12)
Yes	666	89.3	9.8 (2.6, 108)	662	89.2	51 (8)	171	32.6	45 (6)	439	89.8	107 (14)

BSI: Behavior Symptom Index of the Behavioral Assessment System for Children-2; CES-D: Center for Epidemiologic Studies Depression Scale; FSIQ: Full Scale IQ of the Wechsler Preschool and Primary Scales of Intelligence; and SRS-2: Total T-Score from the Social Responsiveness Scale.
[a] This indicates that parenting stress was less than or ≥1 standard deviation above the mean.

and 9.1 ng/mL among women whose children were not followed up (893), followed up in-person or via internet (794), and followed in-person (531), respectively.

The mean BSI, FSIQ, and SRS-2 total scores were 51 (SD:7), 107 (SD:14), and 45 (SD:6), respectively (Table 1). Males had lower mean FSIQ scores, and higher mean BSI and SRS-2 scores compared to females. On average, children born to women who were > 35 years of age, had a graduate degree, were married or living with a partner, employed, and had a household income greater than $100,000 (CAD) had lower BSI and SRS-2 scores and higher FSIQ scores (Table 1).

Associations between prenatal urinary triclosan concentrations and neurobehavioral outcomes were similar before and after adjustment for potential confounders (Table 2). Triclosan was not associated with scores on the BRIEF-P, WPPSI-III summary scales, SRS-2, or NEPSY affect recognition. However, triclosan was associated with less externalizing behaviors; for every 10-fold increase in triclosan, there was a 0.5 point (95% CI: −1.1, 0.0) decrease in scores. Triclosan was associated with better scores on some subscales of the BASC-2 and subtests of the WPPSI-III; for every 10-fold increase in triclosan, there was a 0.6 point (95% CI: −1.2, −0.1) decrease in hyperactivity behavior scores and a 0.2 point (95% CI: 0.0, 0.5) increase in picture completion scores (Table 2).

We did not observe evidence of non-linear relations between triclosan and child neurobehavior. All non-linearity p-values in models containing spline terms were ≥0.1, except for the relationship between triclosan and somatization (p-value = 0.01). However, the 95% CI was

Table 2
Adjusted difference in behavioral and cognitive test score at three years of age with 10-fold increase in specific gravity standardized maternal urinary TCS concentrations during pregnancy: the MIREC study[a,b].

Neurodevelopmental test	N	All children (unadjusted)		All children (adjusted)		Boys		Girls		TCS × sex p-value
		β	95% CI	β	95% CI	β	95% CI	β	95% CI	
BASC-2 summary scales										
BSI	790	−0.3	−0.8, 0.2	−0.3	−0.7, 0.2	−0.5	−1.1, 0.2	−0.1	−0.7, 0.5	0.41
Externalizing	790	−0.6	−1.2, 0.0	−0.5	−1.1, 0.0	−0.7	−1.5, 0.0	−0.1	−0.9, 0.6	0.27
Internalizing	788	−0.3	−0.9, 0.4	−0.2	−0.9, 0.4	−0.3	−1.2, 0.6	−0.3	−1.1, 0.6	0.97
BASC-2 clinical scales										
Hyperactivity	791	−0.7	−1.3, −0.1	−0.6	−1.2, −0.1	−0.7	−1.5, 0.1	−0.5	−1.2, 0.3	0.67
Aggression	790	−0.4	−1.1, 0.2	−0.3	−0.9, 0.3	−0.7	−1.5, 0.2	0.2	−0.7, 1.0	0.16
Anxiety	785	0.3	−0.4, 1.0	0.2	−0.5, 0.9	0.2	−0.9, 1.2	0.1	−0.9, 1.1	0.94
Depression	790	−0.3	−1.0, 0.3	−0.3	−0.9, 0.3	−0.9	−1.7, 0.0	0.1	−0.7, 1.0	0.10
Somatization	790	−0.6	−1.2, 0.0	−0.5	−1.1, 0.1	0.0	−0.9, 0.9	−1.0	−1.9, −0.2	0.10
Atypicality	791	0.0	−0.6, 0.6	0.0	−0.5, 0.6	0.3	−0.5, 1.1	−0.2	−1.0, 0.5	0.35
Withdrawal	788	0.0	−0.7, 0.6	−0.1	−0.8, 0.5	−0.3	−1.3, 0.6	0.0	−0.9, 0.9	0.60
Attention	794	0.1	−0.2, 0.3	0.1	−0.2, 0.3	0.3	−0.1, 0.6	−0.1	−0.5, 0.2	0.16
BRIEF-P										
Working memory	792	−0.5	−1.3, 0.2	−0.3	−1.0, 0.4	−0.2	−1.3, 0.8	−0.5	−1.5, 0.5	0.71
Plan/organize	794	−0.6	−1.3, 0.2	−0.4	−1.1, 0.3	−0.6	−1.6, 0.4	−0.4	−1.4, 0.6	0.79
WPPSI-III summary scales										
FSIQ	528	0.3	−1.0, 1.5	−0.1	−1.2, 1.1	−0.5	−2.1, 1.2	0.2	−1.4, 1.8	0.59
VIQ	526	0.9	−0.3, 2.1	0.6	−0.5, 1.8	0.4	−1.2, 2.0	0.6	−0.9, 2.2	0.88
PIQ	523	−0.5	−1.8, 0.9	−0.8	−2.1, 0.6	−1.2	−3.1, 0.7	−0.5	−2.3, 1.4	0.58
WPPSI-III subtests										
Vocabulary	529	0.1	−0.1, 0.4	0.1	−0.1, 0.4	0.1	−0.3, 0.4	0.1	−0.2, 0.5	0.78
Block design	526	0.0	−0.3, 0.2	−0.1	−0.3, 0.2	−0.1	−0.5, 0.2	0.0	−0.4, 0.3	0.69
Information	518	0.2	−0.1, 0.4	0.1	−0.1, 0.3	0.1	−0.2, 0.4	0.1	−0.2, 0.4	0.90
Object design	526	−0.1	−0.4, 0.2	−0.2	−0.4, 0.1	−0.2	−0.6, 0.1	−0.1	−0.5, 0.2	0.64
Picture completion	527	0.3	0.0, 0.6	0.2	0.0, 0.5	0.4	0.0, 0.7	0.1	−0.3, 0.4	0.23
SRS-2										
Total	524	−0.1	−0.7, 0.4	−0.2	−0.7, 0.3	−0.1	−0.8, 0.6	−0.2	−0.8, 0.4	0.83
Awareness	524	−0.2	−1.0, 0.5	−0.2	−0.9, 0.4	−0.4	−1.3, 0.6	0.0	−0.9, 0.9	0.58
Cognition	524	0.2	−0.4, 0.8	0.1	−0.4, 0.6	0.1	−0.6, 0.8	0.1	−0.5, 0.8	0.95
Communication	524	−0.4	−0.9, 0.2	−0.4	−0.9, 0.1	−0.2	−0.9, 0.5	−0.5	−1.2, 0.1	0.48
Motivation	524	0.0	−0.7, 0.7	−0.1	−0.7, 0.5	−0.1	−1.0, 0.8	−0.2	−1.0, 0.6	0.89
Restricted	524	0.0	−0.7, 0.6	−0.1	−0.6, 0.5	0.0	−0.7, 0.8	−0.1	−0.8, 0.7	0.85
DSM Social	524	−0.1	−0.7, 0.4	−0.2	−0.7, 0.3	−0.1	−0.8, 0.6	−0.2	−0.9, 0.4	0.75
DSM Restricted	524	0.0	−0.7, 0.6	−0.1	−0.6, 0.5	0.0	−0.7, 0.8	−0.1	−0.8, 0.7	0.85
NEPSY: affect recognition	485	0.1	−0.2, 0.3	0.0	−0.2, 0.2	0.0	−0.3, 0.3	0.0	−0.3, 0.3	0.87

BASC-2: Behavioral Assessment System for Children-2; BSI: Behavior Symptom Index of the BASC-2; WPPSI: Wechsler Preschool and Primary Scales of Intelligence-III; FSIQ: Full Scale IQ; VIQ: Verbal IQ; PIQ: Performance IQ; NEPSY: A Developmental Neuropsychological Assessment; and SRS-2: Social Responsiveness Scale.

[a] Adjusted for maternal race, education, age, marital status, employment, household income, smoking during pregnancy, alcohol use during pregnancy, parity, months of exclusive breastfeeding, parental stress, and maternal depressive symptoms.

[b] Positive coefficients for the BASC-2, BRIEF-P, and SRS-2 indicate that TCS concentrations are associated with more behavior problems. Positive coefficients for the WPPSI-III and NEPSY indicate that TCS is associated with better performance.

wide at the tails of the triclosan concentration distribution. When examining quintiles of prenatal urinary triclosan concentrations we did not observe evidence of monotonic dose-response relationships for the notable associations mentioned above (Figs. 1, 2, and 3; Supplemental Table 2). Children born to women in the 2nd, 3rd, 4th, and 5th quintiles of prenatal urinary triclosan concentrations had BASC-2 externalizing scores that were 1.7 (95% CI: −3.0, −0.1), 1.6 (95% CI: −3.0, 0.0), 1.9 (95% CI: −4.0, −0.3), and 2.0 (95% CI: −4.0, −0.4) points lower, respectively, than children born to women in the first quintile (Fig. 1, Supplemental Table 2). No monotonic dose-response relationships were found between prenatal triclosan concentrations and subtest scores on any of the other instruments (results not shown).

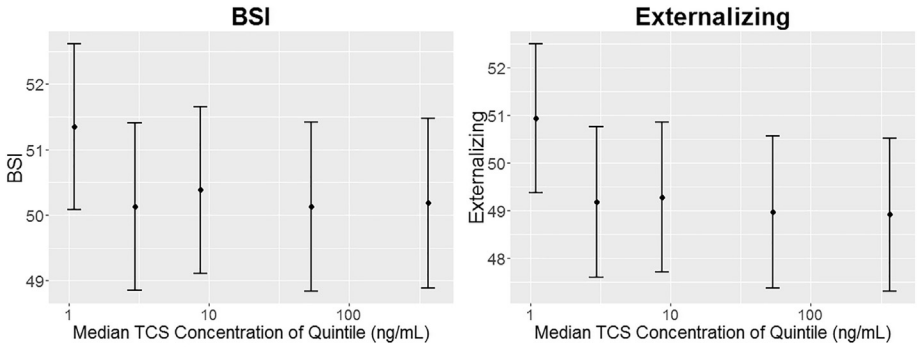
Generally, child sex did not modify the association between prenatal triclosan concentrations and most neurobehavioral scores. However, child sex modified the association between triclosan and two BASC-2 clinical subscales (triclosan × child sex p-values = 0.10). A 10-fold increase in triclosan was associated with a 1.0 point (95% CI: −1.9, −0.2) decrease in somatization scores among girls, but not among boys (β: 0; 95% CI: −0.9, 0.9). A 10-fold increase in triclosan was associated with a 0.9 point (95% CI: −1.7, 0.0) decrease in depression scores among boys, but not girls (β: 0.1; 95% CI: −0.7, 1.0) (Table 2).

3.1. Sensitivity analyses

Folic acid supplement use during pregnancy modified some associations between prenatal urinary triclosan concentrations and neurobehavior at three years of age (triclosan × folic acid supplementation p-value ≤ 0.1); however, only a small number (n = 51) of women did not take folic acid containing supplements during pregnancy, the estimates were imprecise, and the pattern of associations did not consistently show that triclosan was associated with worse neurobehavior among children from women who did not take folic acid supplements (Supplemental Table 3). Adjusting for covariates collected at age 3 years, welfare receipt, child age, or using creatinine-standardized prenatal urinary triclosan concentrations did not appreciably change the results of our analyses (Supplemental Table 4). Among the subset of children who completed the in-person follow-up, adjusting for HOME Inventory scores and daycare use did not appreciably change our results (Supplemental Table 4).

4. Discussion

Prenatal urinary triclosan concentrations during pregnancy were not associated with most neurobehavioral outcomes among 3-year old



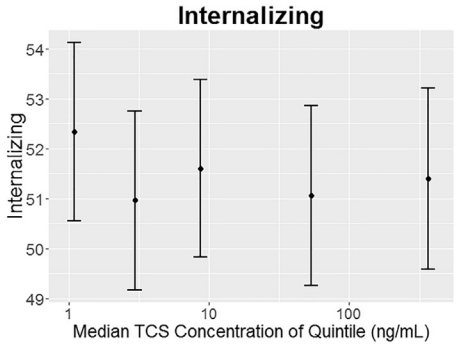
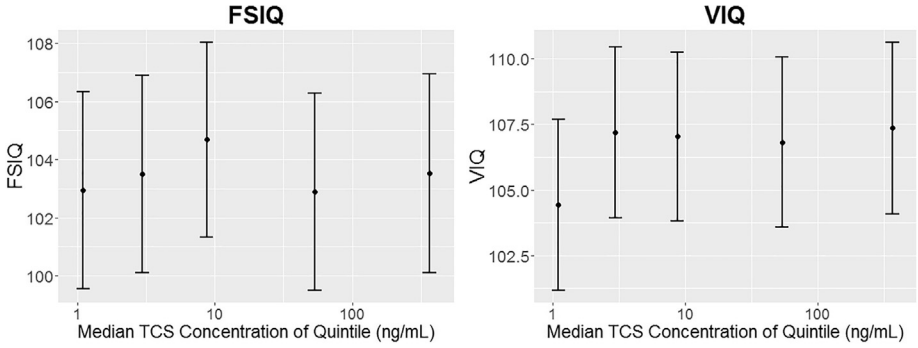


Fig. 1. Covariate adjusted child mean BASC-2 summary scale test scores by maternal urinary triclosan quintile: the MIREC study.
Adjusted for maternal race, education, age, marital status, employment, household income, smoking during pregnancy, alcohol use during pregnancy, parity, months of exclusive breastfeeding, parental stress, and maternal depressive symptoms. Maternal urinary triclosan concentrations are specific gravity standardized. Quintile ranges were 0.17– < 1.9, 1.9– < 5.4, 5.4– < 19, 19– < 179, and 179–2745 ng/mL. Error bars are the 95% confidence intervals. N's are 790, 790, 788 for BSI, Externalizing, and Internalizing, respectively. Note that the y-axis scale changes in each row.



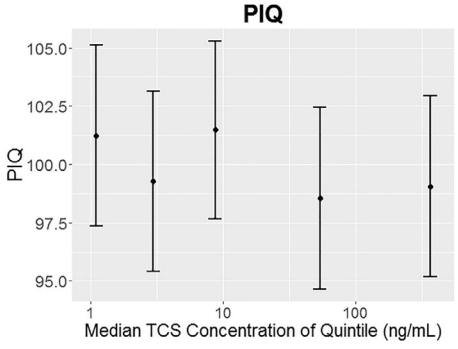


Fig. 2. Covariate adjusted child mean WPPSI-III summary scale test scores by maternal urinary triclosan quintile: the MIREC study.
Adjusted for maternal race, education, age, marital status, employment, household income, smoking during pregnancy, alcohol use during pregnancy, parity, months of exclusive breastfeeding, parental stress, and maternal depressive symptoms. Maternal urinary triclosan concentrations are specific gravity standardized. Quintile ranges were 0.17– < 1.9, 1.9– < 5.4, 5.4– < 19, 19– < 179, and 179–2745 ng/mL. Error bars are the 95% confidence intervals. ‡-N's are 528, 526, and 523 for PSIQ, VIQ, and PIQ, respectively. Note that the y-axis scale changes in each row.

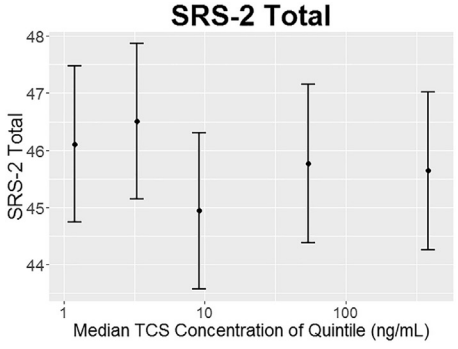


Fig. 3. Covariate adjusted mean child SRS-2 Total and NEPSY test scores by maternal urinary triclosan quintile: the MIREC study.
Adjusted for maternal race, education, age, marital status, employment, household income, smoking during pregnancy, alcohol use during pregnancy, parity, household income, months of exclusive breastfeeding, parental stress, and maternal depressive symptoms. Maternal urinary triclosan concentrations are specific gravity standardized. Quintile ranges were 0.17– < 2.0, 2.0– < 5.8, 5. 8– < 21, 21– < 189, and 189–2745 ng/mL. Error bars are the 95% confidence intervals. N's are 524 for SRS-2 Total and 485 NEPSY. Note that the y-axis scale changes in each row.

children in this cohort. However, higher urinary triclosan concentrations during pregnancy were weakly associated with better parent-reported externalizing and hyperactivity scores, and picture completion scores. In general, the relationships between prenatal urinary triclosan concentrations and most neurobehavioral outcomes were not modified by child sex. A strength of this study is the large sample size, which allowed us to precisely estimate the presence of associations among all children, and boys and girls separately.

We are aware of only one epidemiological study examining the association between prenatal triclosan exposure and neurodevelopment. Braun et al. found that prenatal urinary triclosan concentrations were not associated with visual-spatial abilities among 8-year-old children, nor were associations modified by child sex (Braun et al., 2017b). This study had two urine samples collected at 16 and 26 weeks of pregnancy and median prenatal urinary triclosan concentrations were slightly higher than median concentrations in this study (18 vs. 13 μg/g Cr).

Previous in vitro research has shown that triclosan exposure can induce apoptosis in neocortical neurons by activating and stimulating apoptotic signaling pathways and inducing the aryl hydrocarbon receptor (AhR)-dependent apoptosis through impairment of Cyp1a1 signaling and transcriptional activity of AhR (Szychowski et al., 2015; Szychowski et al., 2016). Prenatal triclosan exposure may also affect neurodevelopment by reducing levels of thyroid hormones during pregnancy as suggested by multiple animal studies (Paul et al., 2012; Paul et al., 2010) and a two studies of pregnant women and their infants (Wang et al., 2017; Braun et al., 2017a). Given the potential for triclosan to disrupt thyroid hormone homeostasis in pregnant women and the neonate, future epidemiological studies could examine thyroid hormone levels as an outcome and determine if thyroid hormones mediate any associations between prenatal triclosan exposure and child neurobehavior.

Our null findings could be attributed to triclosan exposure misclassification. Triclosan has a short half-life (< 24 h) and exposures are episodic in nature. Thus, having one urine sample during the first trimester of pregnancy could have resulted in exposure misclassification. Given that urinary triclosan concentrations have good reproducibility over the course of a day (intraclass correlation coefficient (ICC) of 0.77–0.79) (Perrier et al., 2016) and moderate over the pregnancy (Perrier et al., 2016; Schug et al., 2015), it is possible our results are attenuated towards the null, assuming non-differential exposure misclassification. Furthermore, in a cohort of pregnant Canadian women similar to MIREC, a single spot urine sample collected at any time during or post-pregnancy was able to predict a participant's geometric mean urinary TCS level corresponding to low, medium, or high exposure with 86.7% accuracy (Perrier et al., 2016). The extent of the misclassification would depend on the duration of the critical window of exposure. A simulation study found that under certain assumptions, associations between health outcomes and urinary biomarker concentrations with intraclass correlation coefficients of ~0.6 can be attenuated towards the null by 40, 25, and 18% when one, two, or three urine samples, respectively are pooled prior to laboratory analysis (Perrier et al., 2016). Future studies could use measurement error correction methods described by Perrier and others to “dis-attenuate” associations between non-persistent chemical biomarkers and health outcomes.

In addition, the timing of our exposure assessment may have led to null results if the critical window of exposure was later in gestation or in the post-natal period. Due to funding limitations we were only able to quantify triclosan concentrations in one urine sample during the first trimester of pregnancy. Other neurodevelopmental processes that occur later in gestation or during childhood (e.g., myelination) may be more sensitive to triclosan exposure (Schug et al., 2015), but we were unable to examine those associations. Finally, we may have missed an association between prenatal triclosan exposure and neurobehavior if the effects do not manifest until later in life or if they are traits that develop later in childhood (e.g., executive function and anxiety). Some prior studies examining other toxicant-associated alterations in child neurobehavior have observed that these associations may not manifest until later in childhood (Chen et al., 2014; Braun et al., 2017c).

A strength of this study is that we comprehensively assessed numerous features of children's behaviors and cognitive abilities at three years of age. Moreover, both interviewers and parents were blinded to the mother's triclosan concentrations.

There are some limitations of this study that should be acknowledged. First, not all children completed the follow-up portions of the study due to budgetary and logistic constraints, and there was loss to follow-up of some participants. Mothers of children that did not complete the follow-up were more likely to be younger, non-White, less educated, and have lower household income than mothers of children who did not complete follow-up. While those lost to follow-up may also be more likely to have adverse neurodevelopment, prenatal triclosan concentrations at baseline did not differ among those with and without follow-up. Second, while we adjusted for many potential confounders, which did not appreciably change our results, there is the possibility of residual confounding from other factors associated with both triclosan exposure and child neurobehavior. For instance, women with higher education had higher urinary triclosan concentrations and their children had better behavioral and cognitive ability scores, which could produce negative confounding (biased towards the null). While we observed negative confounding in a prior study examining the association between prenatal triclosan exposure and neonatal outcomes (Etzel et al., 2017), we did not find evidence of it in this study. The absence of appreciable confounding from sociodemographic factors in these data may be due to less variation in these factors among MIREC women. While the MIREC cohort is relatively homogenous with regards to sociodemographic features, and this is advantageous with regards to potential confounding, it may limit the generalizability of these results. Finally, we did not measure maternal IQ. While maternal education is a reasonable proxy of IQ, having a measurement of maternal IQ may also be important to explain additional variation in child IQ not explained by maternal education.

5. Conclusions

We found few notable associations between a single measurement of prenatal urinary triclosan concentrations and multiple features of child behavior and cognitive abilities at three years of age in the MIREC cohort. Given the potential for environmental exposures to impact neurodevelopment and potential limitations of this study including the use of only a single triclosan measurement during early pregnancy, future studies should test these associations using repeated measures of triclosan exposure during pregnancy and childhood to determine if there are particular periods of heightened vulnerability to triclosan exposure.

Funding sources

This work was supported by National Institute of Environmental Health Sciences (R01 ES024381); Health Canada's Chemicals Management Plan; Canadian Institute of Health Research (Grant # MOP-81285); and Ontario Ministry of the Environment.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.02.032.

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